IN THE DISTRICT COURT
SOUTHERN DISTRICT OF GEORGIA
WAYCROSS DIVISION

CASE NO.: CV506-075

WILLIAM GRIFFIN, widower,
and as PERSONAL REPRESENTATIVE
OF THE ESTATE OF SHIRLEY GRIFFIN,
deceased,

Plaintiff,

vs.

PFIZER, INC., a foreign corporation,

Defendant.
_____/

COMPLAINT AND JURY DEMAND

COMES NOW the Plaintiff, William Griffin, widower, and as a Personal Representative of the Estate of Shirley Griffin, by and through her undersigned attorneys, and brings this action against Defendant, Pfizer, Inc., and alleges as follows:

JURISDICTIONAL ALLEGATIONS AND PARTIES

1. This is an action for damages, which exceeds Seventy-Five Thousand Dollars ($75,000), relating to Defendant's design, manufacture, sale, testing, marketing, advertising, promotion and/or distribution of the unsafe medication Bextra®. Plaintiff alleges this is wrongful death action for damages, excluding fees and costs, that exceed $75,000.00.

2. Plaintiff, William Griffin, is Personal Representative of the Estate of Shirley Griffin, deceased, and accordingly is the proper person to bring this lawsuit to recover damages for her death.

3. At the time of her death, William and Shirley Griffin were legally husband and wife and resided in the State of Georgia.

4. The following are survivors and beneficiaries of a recovery for the wrongful death of Shirley Griffin:

a) William Griffin, husband;

b) Sylvia Curl, daughter;

c) Darryl M. Griffin, son;

d) The Estate of Shirley Griffin;

5. Defendant, Pfizer, Inc. ("Pfizer") is a Delaware corporation that maintains a principal place of business at 235 East 42nd Street, New York, New York. At all times material, Pfizer was authorized to conduct business in the State of Georgia.

6. There is complete diversity of citizenship between the Plaintiff and the Defendant. This Honorable Court has subject matter jurisdiction over this matter pursuant to 28 U.S.C.A. § 1332 (Diversity Jurisdiction), because the amount in controversy exceeds $75,000.00 and there is complete diversity of citizenship between Plaintiff and Defendant.

7. Pfizer is subject to the long-arm jurisdiction of this state pursuant to OCGA § 9-10-91, by reason of the following:

a. Pfizer operated, conducted, engaged in and/or carried on a business or business venture in this state or had an office or agency in this state (OCGA § 9-10-91 (1));

b. Pfizer committed a tortious act within this state (OCGA § 9-10-91 (2));

c. Pfizer caused injury to persons within this state arising out of an act or omission by Defendant outside this state when, at or about the time of the injury, the Defendant was engaged in solicitation or service activities within this state and products, materials or things processed, serviced or manufactured by the Defendant anywhere were used or consumed within this state in the ordinary course of commerce, trade or use. (OCGA § 9-10-91 (3)); and

d. Pfizer engaged in substantial and not isolated activity within this state (OCGA § 9-10-91 (3)).

8. Pfizer committed a tort within the State of Georgia and may be served with process in accordance with Rule 4 of the Federal Rules of Civil Procedure, through its registered agent for service of process.

9. At all times material, Defendant was engaged in the manufacturing, packaging, marketing, distributing, promoting and the sale of the drug valdecoxib, under the trade name Bextra®.

10. This action arises out of the Defendants' manufacturing, selling, distributing, marketing and/or otherwise promoting Bextra without notice to potential consumers of the dangers associated

with ingestion of this drug. Defendant continues to transact substantial business in the State of Georgia.

11. The Plaintiff was prescribed, or otherwise lawfully provided with, Bextra in the State of Georgia.

12. Defendant derives substantial revenue from pharmaceutical products used or consumed in the State of Georgia. Defendant expected, or should have expected, that its business activities could have consequences within the State of Georgia.

13. Venue is proper in this United States Judicial District pursuant to 28 U.S.C.A. § 1391. Plaintiff purchased the product, Bextra, in this District of Georgia and resides in this district, and Defendant marketed, advertised and distributed Bextra in this district, thereby receiving substantial financial benefit and profits from the product, Bextra, in this district.

FACTUAL BACKGROUND

14. As a direct and proximate result of Defendant's negligence, as described herein, Shirley Griffin died November 26, 2004, as a result of ingesting Bextra when she suffered a heart attack caused by Bextra.

15. Bextra (Valdecoxib) is a prescription drug designed to treat pain through reduced inflammation agent (NSAID). Defendant, Pfizer, did develop, manufacture, design, package, market, sell and distribute this drug in the State of Georgia at all times relevant to this action.

16. At the time Defendant developed and manufactured Bextra, Defendant intended to capture a portion of the consumer market for cox-2 specific inhibitors.

17. The scientific data available during and after Pfizer's approval process should have alerted Pfizer that its formulation of Bextra could cause a higher risk of blood clotting, stroke and/or myocardial infarctions among Bextra consumers.

18. Despite the findings, Pfizer continued to conceal or minimize the cardiovascular risks associated with Bextra use.

19. Pfizer had control over the design, manufacturing, assembly, labeling, warning,

packaging, marketing, advertising, promotion, direct-to consumer advertising, and/or sale of the drug Bextra.

20. At all times material, Pfizer actually knew of the defective nature of its product, Bextra, yet continued to design, manufacture, market, promote, distribute and sell its product so as to maximize company sales and profits at the expense of consumer safety and health and in conscious disregard of the foreseeable harm caused by Bextra.

21. Although Pfizer knew or should have known that dangerous cardiovascular risks were associated with the use of Bextra, it continued on its aggressive marketing campaign and continued to manufacture, package, distribute, promote and sell Bextra without adequate warnings of the serious side effect and risks.

22. Plaintiff did not know of the potential connection between the use of Bextra and his wife's death until after the Food & Drug Administration ("FDA") issued its recommendation, on April 7, 2005, that Bextra be withdrawn from the market.

23. Decedent, Shirley Griffin, used Bextra for its intended purpose.

24. Decedent, Shirley Griffin, was not warned that Bextra was dangerous to her health.

COUNT I
STRICT LIABILITY

25. Plaintiff incorporates by reference paragraphs 1 through 24 above.

26. Bextra was defective and unreasonably dangerous when it left the possession of the Defendant, Pfizer, in that:

a. When placed in the stream of commerce, Bextra contained unreasonable dangers, design defects and was not reasonably safe as intended to be used, subjecting Plaintiff to risks which exceeded the benefits of the drugs;

b. When placed in the stream of commerce, Bextra was defective in design and formulation, making use of the drug more dangerous than an ordinary consumer would expect and more dangerous than other risks associated with Plaintiff's conditions;

c. Bextra contained insufficient warnings to alert consumers, the consumer's prescribing physicians and users of the severe, life-threatening complications and side effects, including but not limited

to stroke and adverse cardiovascular events;

d. There was misleading advertising and promotion concerning the benefits of using Bextra and;

e. There are inadequate post-marketing warnings or instructions, because Pfizer knew or should have known of the significant risks associated with the use of Bextra, Pfizer failed to provide adequate warnings to consumers and the consumer's prescribing physicians and Pfizer continued to aggressively promote and advertise, direct to consumers, the sale and use of the drug.

27. Decedent, Shirley Griffin, used Bextra for its intended purpose.

28. The Bextra products, sold to Decedent, Shirley Griffin, reached the Decedent without substantial change. Decedent, Shirley Griffin, was unaware of the dangerous propensities of the product at the time he ingested Bextra.

29. Decedent, Shirley Griffin, ingested the Bextra without making any changes or material alterations to the product.

30. Prescribing physicians do not have substantially the same knowledge as manufacturers regarding prescription medication. Prescribing physicians rely on manufacturers to provide adequate and appropriate warning regarding their products.

31. Pfizer had a continuing duty to provide accurate and adequate warnings to prescribing physicians of the dangers, risks and reactions associated with the use of Bextra.

32. The warnings given by Pfizer, to prescribing physicians, regarding Bextra were deficient, inadequate, unclear, misleading and/or ambiguous.

33. Decedent, Shirley Griffin, could not have discovered any defects in Bextra through the exercise of due care.

34. As a direct and legal result of the defective condition of the drug Bextra, Shirley Griffin died prematurely, and the survivors have, to the extent governed by OCGA § 51-4-2, *et seq.*, ("Georgia Wrongful Death Act"), sustained the loss of Shirley Griffin's support and services, companionship and protection, while continuing to endure mental pain and suffering, anguish and emotional distress.

35. As a result of the premature death of Shirley Griffin, the Estate of Shirley Griffin has sustained the costs of medical and funeral expenses, loss of earnings, net accumulations, the full value of the life of Shirley Griffin and other damages permitted by law.

WHEREFORE, Plaintiff demands judgment against Pfizer, Inc., for damages and costs in a sum in excess of the jurisdictional requirement of this court.

COUNT II
NEGLIGENCE

36. Plaintiff incorporates by reference paragraphs 1 through 35 above.

37. At all times material hereto, Pfizer had a duty to exercise reasonable care in the design, manufacture, testing, processing, labeling, packaging, advertising, marketing, distribution and sale of its products.

38. Pfizer knew or should have known that Bextra caused unreasonably dangerous risks and serious side effects. Despite such knowledge, Pfizer aggressively advertised, marketed, sold and distributed Bextra, knowing that there were safer methods and products for use with pain and inflammation.

39. Pfizer was negligent and breached its duty in the following manner:

a. Pfizer failed to adequately and properly test its drug product, Bextra before placing Bextra on the market;

b. Pfizer failed to adequately, accurately and appropriately warn prescribing physicians of the significant risk of cardiovascular events associated with the use of Bextra.

c. Pfizer concealed the dangerous properties of Bextra in order to increase Pfizer's market share.

40. As a direct and legal result of the defective condition of the drug Bextra, Shirley Griffin died prematurely, and the survivors have, to the extent governed by OCGA § 51-4-2, *et seq.*, ("Georgia Wrongful Death Act"), sustained the loss of Shirley Griffin's support and services, companionship and protection, while continuing to endure mental pain and suffering, anguish and emotional distress.

41. As a result of the premature death of Shirley Griffin, the Estate of Shirley Griffin has

sustained the costs of medical and funeral expenses, loss of earnings, net accumulations, the full value of the life of Shirley Griffin and other damages permitted by law.

WHEREFORE, Plaintiff demands judgment against Pfizer, Inc., for damages and costs in a sum in excess of the jurisdictional requirement of this court.

COUNT III
NEGLIGENT MISREPRESENTATION

42. Plaintiff incorporates by reference paragraphs 1 through 41 above.

43. At all times material hereto, Pfizer knew or should have known that its prescription medication, Bextra, caused unreasonable dangers, risks and serious side effects.

44. Despite its knowledge, Pfizer aggressively advertised, marketed, sold and distributed Bextra knowing there were safer methods and products for use with pain and inflammation.

45. Pfizer negligently misrepresented to the Decedent, Shirley Griffin, and her prescribing physician the safety and effectiveness of Bextra and/or negligently misrepresented material information regarding the drug and/or negligently misrepresented adverse information regarding the safety and effectiveness of Bextra.

46. Pfizer's misrepresentations were communicated to Decedent, Shirley Griffin's, prescribing physician with the intent that they reach the Decedent and that the effect of such representations would be that prescriptions would be written for the drug consuming public, including Decedent.

47. Pfizer made these representations and actively concealed adverse information at a time when the Defendant knew, or should have known, that its drug product had defects, dangers, and characteristics that were other than what Pfizer and its representatives had represented to prescribing physicians or other dispensing entities, the FDA and the consuming public, including Decedent, Shirley Griffin.

48. The misrepresentations of Pfizer were perpetuated directly and/or indirectly by Pfizer and its employees, agents and/or other detail persons.

49. The misrepresentations by Pfizer constitute a continuing tort.

50. Pfizer had a continuing duty to warn Decedent, Shirley Griffin, and/or Decedent's prescribing physicians in a timely manner about the potential risks and complications associated with Bextra.

51. As a direct and legal result of the negligent misrepresentation of Pfizer, Shirley Griffin died prematurely, and the survivors have, to the extent governed by OCGA § 51-4-2, *et seq.*, ("Georgia Wrongful Death Act"), sustained the loss of Shirley Griffin's support and services, companionship and protection, while continuing to endure mental pain and suffering, anguish and emotional distress.

52. As a result of the premature death of Shirley Griffin, the Estate of Shirley Griffin has sustained the costs of medical and funeral expenses, loss of earnings, net accumulations, the full value of the life of Shirley Griffin and other damages permitted by law.

WHEREFORE, Plaintiff demands judgment against Pfizer, Inc., for damages and costs in a sum in excess of the jurisdictional requirement of this court.

COUNT IV
FRAUD

53. Plaintiff incorporates by reference paragraphs 1 through 52 above.

54. Pfizer fraudulently or intentionally misrepresented to the Decedent, Shirley Griffin, and/or Decedent's prescribing physician the safety and effectiveness of Bextra and/or fraudulently or intentionally concealed material information regarding the drug and/or fraudulently or intentionally misrepresented adverse information regarding the safety and effectiveness of the drug.

55. Pfizer fraudulently or intentionally communicated misrepresentations to Decedent's prescribing physicians with the intent that they reach the Decedent.

56. Pfizer knew that its representations were false.

57. Decedent's prescribing physician and Decedent relied on the representations of Pfizer and approved the continuing use of Bextra by Decedent.

58. Pfizer made the fraudulent or intentional misrepresentation and/or actively concealed adverse information with the intention and specific desire that the Decedent, Shirley Griffin, the

Decedent's prescribing physician and/or dispensing entities and the consuming public would rely on such false information in selecting Bextra for treatment of pain and inflammation.

59. Pfizer made the fraudulent or intentional misrepresentations and actively concealed adverse information at a time when they knew that Bextra had defects, dangers and characteristics that were other than what Pfizer had represented to the prescribing physician or other dispensing entities, the FDA and the consuming public, including Decedent. Specifically, Pfizer fraudulently or intentionally misrepresented to and/or actively concealed from Decedent, Decedent's prescribing physician or other dispensing entities, the FDA and the consuming public the following adverse information regarding the drug Bextra, as ingested by Decedent:

a. That Bextra carried risks of serious adverse effects;

b. Despite knowing that there were serious risks of adverse cardiovascular events, Pfizer aggressively marketed, promoted advertising direct to consumer and/or sold the drug as if there was no risk;

c. Failed to advise Decedent, Decedent's prescribing physicians and others that prior studies, research, reports and/or testing had been conducted linking the use of the drug to serious adverse cardiovascular events;

d. Represented that Bextra was safer than other alternative medications and fraudulently concealed information, which demonstrated that Bextra was not safer than alternatives available on the market.

60. The fraudulent or intentional misrepresentation and/or concealment by Pfizer constitute a continuing tort.

61. Pfizer had a continuing duty to warn Decedent and Decedent's prescribing physicians of the drug product in their labeling, advertising, product inserts, promotional material, direct to consumer advertising or other marketing efforts.

62. Pfizer fraudulently and intentionally misrepresented the safety and efficacy of Bextra in their labeling, advertising, product insert, promotional material, direct-consumer advertising or other marketing efforts.

63. Decedent and Decedent's prescribing physicians and dispensing entities justifiably relied

to their detriment on and/or were induced by the fraudulent or intentional misrepresentations and/or concealment by Pfizer regarding the safety and effectiveness of Bextra.

64. As a direct and legal result of the fraudulent and intentional misrepresentation of Pfizer Shirley Griffin died prematurely, and the survivors have, to the extent governed by OCGA § 51-4-2, *et seq.*, ("Georgia Wrongful Death Act"), sustained the loss of Shirley Griffin's support and services, companionship and protection, while continuing to endure mental pain and suffering, anguish and emotional distress.

65. As a result of the premature death of Shirley Griffin, the Estate of Shirley Griffin has sustained the costs of medical and funeral expenses, loss of earnings, net accumulations, the full value of the life of Shirley Griffin and other damages permitted by law.

WHEREFORE, Plaintiff demands judgment against Pfizer, Inc., for damages and costs in a sum in excess of the jurisdictional requirement of this court.

COUNT V
VIOLATION OF THE GEORGIA DECEPTIVE AND UNFAIR TRADE PRACTICES ACT

66. Plaintiff incorporates by reference paragraphs 1 through 24 above.

67. This is an action brought pursuant to Georgia Deceptive and Unfair Trade Practices Act contained at OCGA Article 15 of Chapter 1 of Title 10, *et seq*.

68. Pfizer, through its agents, servants and employees, employed deception, fraud, false pretense, false promise, misrepresentation, unfair practice and the concealment, suppression and omission of material facts, in connection with the sale and/or advertisement of Bextra.

69. Such false and unfair practices violate the Georgia Deceptive and Unfair Trade Practices Act which makes it unlawful to engage in unfair methods of competition, unconscionable acts or practices and unfair or deceptive acts or practices in the conduct of any trade or commerce. OCGA Article 15 of Chapter 1 of Title 10.

70. As a direct and legal result of the foregoing, Shirley Griffin died prematurely, and the survivors have, to the extent governed by OCGA § 51-4-2, *et seq.*, ("Georgia Wrongful Death Act"),

sustained the loss of Shirley Griffin's support and services, companionship and protection, while continuing to endure mental pain and suffering, anguish and emotional distress.

71. Pursuant to Article 15 of Chapter 1 of Title 10 of the Official Code of Georgia Annotated of the Georgia Deceptive and Unfair Trade Practices Act, Plaintiff seeks the actual damages plus attorneys' fees and court costs for Pfizer's conduct that resulted in the premature death of Shirley Griffin, resulting in the Estate of Shirley Griffin sustaining the costs of medical and funeral expenses, loss of earnings, net accumulations, the full value of the life of Shirley Griffin and other damages permitted by law.

WHEREFORE, Plaintiff demands judgment against Pfizer, Inc., for damages and costs in a sum in excess of the jurisdictional requirement of this court.

DEMAND FOR TRIAL BY JURY AND COSTS

Plaintiff, William Griffin, widower, and as Personal Representative of the Estate of Shirley Griffin, deceased, hereby demands a trial by jury of all issues herein so triable and, in addition, demands an award of attorneys' fees and costs incurred in prosecuting this action.

SPOHRER, WILNER, MAXWELL & MATTHEWS, P.A.

Roger J. Dodd, Esquire
Georgia Bar No. 224300
Florida Bar No. 0282041
Floyd L. Matthews, Jr., Esquire
Florida Bar No. 182511
701 W. Adams St.
Jacksonville FL 32204
(904) 354-8310 Telephone
(904) 358-6889 Facsimile
email: fmatthews@swmmlaw.com
and
Donald Black, Esquire
Florida Bar No. 227791
Harrell & Harrell
4735 Sunbeam Road
Jacksonville, FL 32257

Attorneys for Plaintiff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Raymond V. Gilmartin
President and CEO
Merck & Co., Inc.
P.O. Box 1000, UG3BC-10
North Wales, PA 19454-1099

SEP 17 2001

RE: NDA 21-042
Vioxx (rofecoxib) tablets
MACMIS ID # 9456

WARNING LETTER

Dear Mr. Gilmartin:

This Warning Letter concerns Merck & Co. Inc.'s (Merck) promotional activities and materials for the marketing of Vioxx (rofecoxib) tablets. Specifically, we refer to promotional audio conferences given on behalf of Merck by Peter Holt, MD, a press release, and oral representations made by Merck sales representatives to promote Vioxx. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and applicable regulations. See 21 U.S.C. §§ 331(a) and (b), 352(a), (f), and (n), and 355-(a).

You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresents the safety profile for Vioxx. Specifically, your promotional campaign discounts the fact that in the VIGOR study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug (NSAID), Naprosyn (naproxen).

Although the exact reason for the increased rate of MIs observed in the Vioxx treatment group is unknown, your promotional campaign selectively presents the following hypothetical explanation for the observed increase in MIs. You assert that Vioxx does not increase the risk of MIs and that the VIGOR finding is consistent with naproxen's ability to block platelet aggregation like aspirin. That is a possible explanation, but you fail to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that Vioxx may have pro-thrombotic properties.

You have also engaged in promotional activities that minimize the Vioxx / Coumadin (warfarin) drug interaction, omit important risk information, make unsubstantiated superiority claims against other NSAIDs, and promote Vioxx for unapproved uses and an unapproved dosing regimen. In addition, in misrepresenting the Vioxx / warfarin drug interaction you also misrepresent Vioxx's safety profile by minimizing the potentially serious risk of significant bleeding that can result from using Vioxx and warfarin concomitantly.

Your minimizing these potential risks and misrepresenting the safety profile for Vioxx raise significant public health and safety concerns. Your misrepresentation of the safety profile for Vioxx is particularly troublesome because we have previously, in an untitled letter, objected to promotional materials for Vioxx that also misrepresented Vioxx's safety profile.

Background

Vioxx is a NSAID with selective cyclooxygenase 2 (COX-2) inhibitory properties. It was approved on May 20, 1999, for the treatment of primary dysmenorrhea, for the management of acute pain in adults, and for relief of the signs and symptoms of osteoarthritis.

Prior to approval, endoscopy studies were submitted to the original NDA database demonstrating that treatment with Vioxx 25 mg or 50 mg daily was associated with a significantly lower percentage of endoscopically apparent gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. Because the correlation between findings of endoscopic studies and the relative incidence of clinically serious upper gastrointestinal (GI) events was unknown, after approval, Merck sponsored the VIGOR study to obtain information regarding clinically meaningful upper GI events and to develop a large controlled database for overall safety assessment.

The VIGOR study included approximately 4000 patients per treatment arm (Vioxx 50 mg a day or naproxen 1000 mg a day) treated for a median time of 9 months. The primary endpoint of the study was the relative risk of confirmed PUBs (perforations, symptomatic ulcers, and GI bleeds) in patients with rheumatoid arthritis taking Vioxx 50 mg daily (two to four times the approved dosing regimen for Vioxx in osteoarthritis), compared to patients taking naproxen, 1000 mg daily. The study also compared the safety and tolerability of the two treatments in patients with rheumatoid arthritis. The results of the study demonstrated that patients on Vioxx had a significantly lower cumulative incidence of PUB's compared to patients on naproxen (2.08% and 4.49% for Vioxx and naproxen, respectively).

Other important results from the VIGOR study included the unexpected findings that investigator reported serious cardiovascular events occurred in 101 patients (2.5%) in the Vioxx treatment group compared to 46 patients (1.1 %) in the naproxen treatment group, and MIs occurred in 20 patients among 4047 in the Vioxx treatment group (0.5%), compared to four patients among 4029 in the naproxen treatment group (0.1%). These unexpected findings were extensively discussed at the FDA Arthritis Advisory Committee Meeting on February 8, 2001. Although, the reason for these differences is not clear, possible explanations include both an ability of naproxen to function as a cardioprotective agent and a pro-thrombotic property of Vioxx.

Raymond V. Gilmartin
Merck & Co., Inc.
NDA 21-042

Promotional Audio Conferences

We are aware of six promotional audio conferences, presented on behalf of Merck by Peter Holt, MD that are in violation of the Act and its implementing regulations. These audio conferences were held on June 8, 2000, June 13, 2000, June 16, 2000, and three on June 21, 2000, and were moderated by Merck employees.

On December 12, 2000, we sent you a written inquiry about your involvement with and influence on the initiation, preparation, development, and publication of audio conferences given by Dr. Holt. We also asked you to describe the nature of the relationship between you and Dr. Holt. In your response dated January 5, 2001, you stated that, "Dr. Holt entered into a speaker contract with Merck on June 22, 1999." You also stated that, "Merck has determined that we arranged for Dr. Holt to speak at ten audio conferences in 2000. Merck Business Managers provided him with the topic for the audio conferences and, for two of the audio conferences, asked him to address the safety profiles of Vioxx and other NSAIDs."

The promotional audio conferences identified above, arranged by, and presented on behalf of, Merck were false or misleading in that they minimized the MI results of the VIGOR study, minimized the Vioxx / Coumadin drug interaction, omitted important risk information, made unsubstantiated superiority claims, and promoted Vioxx for unapproved uses and an unapproved dosing regimen. Our specific objections follow.

Minimization of MI Results

Statements made during the promotional audio conferences identified above minimize the potentially serious MI risk that may be associated with Vioxx therapy. For example, in your June 21, 2000, audio conference you begin your discussion of the MI rates observed in the VIGOR study by stating, "When you looked at the MI rate the rate was different for the two groups. The MI rate for Vioxx was 0.4 percent and if you looked at the Naprosyn arm it was 0.1 percent, so there was a reduction in MIs in the Naprosyn group." You then present your explanation as to why the Vioxx treatment arm had an increased rate of MIs compared to the naproxen treatment arm. Specifically, you state that,

> Vioxx is a wonderful, effective, selective COX-2 inhibitor that inhibits COX-2 but at the doses used does not inhibit COX-1. So therefore without the COX-1 inhibition you don't inhibit platelets, you don't prolong bleeding time and therefore it cannot be used as a cardiovascular protective drug. Naprosyn on the other hand is a wonderful platelet inhibitor, prolongs bleeding time and inhibits platelets identically to aspirin. Obviously the binding with Naprosyn is reversible and with aspirin is irreversible, but the effect on platelets and bleeding time is identical in terms of its effect and therefore functions as a wonderful drug for cardiovascular prophylaxis. So basically the MI rates are in sync with what we know about Vioxx and what we know about Naprosyn.

In fact, the situation is not at all clear. There are no adequate and well-controlled studies of naproxen that support your assertion that naproxen's transient inhibition of platelet aggregation is pharmacodynamically comparable to aspirin or clinically effective in decreasing the risk of MIs. Therefore, your representation that naproxen prolongs bleeding time and inhibits platelets identically to aspirin is misleading, and minimizes the potential seriousness of this finding. As you know, the

reason for the difference between Vioxx and naproxen has not been determined; it is also possible that Vioxx has pro-thrombotic properties. Also, the MI rate that you report for Vioxx is inaccurate; the MI rate for Vioxx in the VIGOR study was 20 MIs among 4047 patients (0.5%), not 0.4%, as you stated.

Your minimization of the seriousness of the MI rates observed in the Vioxx treatment arm of the VIGOR trial is further reinforced in your audio conferences by your discussion of a retrospective analysis of this trial. For example, in your June 21, 2000, audio conference, you state that,

> ...Merck went and pulled out those patients that again were enrolled in VIGOR and asked the question, who were those patients that really needed secondary cardiovascular prophylaxis from the get go, and that ended up being four percent of the study group in VIGOR based on whether there was a prior MI, stroke, TIA, angina, CABG or PTCA....Now if you look at the remaining part of VIGOR, which is 96 percent of the VIGOR population, and once again looked for the MI rate between Naprosyn and Vioxx, there's no statistically significant difference in the MI rate between Naprosyn and Vioxx. In fact, Naprosyn is 0.2 percent and Vioxx is 0.1 percent.

Your claim that the MI rate for naproxen was 0.2 percent and for Vioxx was 0.1 percent is again inaccurate. Contrary to your claim that there was a higher rate of MIs in the naproxen group compared to the Vioxx group, the MI rate for Vioxx in this subpopulation was 12 MIs among 3877 patients (0.3%) as compared to 4 MIs among 3876 patients (0.1%) for naproxen.

Moreover, you again minimize the Vioxx MI rate observed in the VIGOR study by your comparison of this rate to the rate of MIs observed for Celebrex (celecoxib) in the Celebrex Long-Term Arthritis Safety Study (CLASS). For example, in your June 21, 2000, audio conference you state, "Now if you remember the crude MI rate of Vioxx in VIGOR that number was 0.4 percent which is basically the same or in fact a little bit less then the crude MI rate of Celebrex in CLASS which is 0.5 percent." Your claim that the MI rates of Vioxx compared to Celebrex were basically the same, "or in fact a little bit less" is misleading. You are comparing MI rates from two different trials with different patient populations. For example, patients who had angina or congestive heart failure with symptoms that occurred at rest or minimal activity and patients taking aspirin, including low-dose (325 mg or less, daily or every other day) or other antiplatelet agents (e.g., ticlopidine) were excluded from the VIGOR trial. The CLASS trial in contrast, did not exclude patients of this type. The CLASS trial thus may have included patients at a higher risk for MIs.

Minimization of Vioxx / Coumadin Interaction

Statements made during your promotional audio conferences also minimize the risk of Vioxx therapy in patients who are taking warfarin. For example, in your June 16, 2000, audio conference you stated that, "...if you look at the thromboembolic events it's very clear that these selective COX-2 inhibitors have the benefit of not having platelet aggregation and bleeding time, and therefore, can be used safely in terms of post-op and with Coumadin." Your statement that Vioxx can be used safely with warfarin minimizes the precaution in the PI that states that "...in post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving Vioxx concurrently with warfarin." Your promotion minimizing the risk of using Vioxx and warfarin concurrently is particularly troublesome because Merck was aware of this potentially dangerous drug interaction in 1999, well before these audio conferences occurred. In fact,

Merck began disseminating a revised PI in October 1999, which included new information about this risk.

The seriousness of this interaction is further minimized by your suggestion that COX-2 inhibitors, including Vioxx, can be used safely with warfarin because it "has the benefit of not having platelet aggregation and bleeding time." This claim implies that Vioxx is safer than other NSAIDS used in combination with warfarin. However, Vioxx has not been studied in head-to-head trials prospectively designed to assess this specific endpoint. Your superiority claim is therefore misleading.

We note that earlier in your June 16, 2000, promotional audio conference you state, "It can be used in people with Coumadin, although with Coumadin you've got to check their INR three and four days after you add the Cox inhibitor to the Coumadin because there may be a bump in the INR." This disclosure does not correct the overall misleading message, however, nor does it correct your suggestion that Vioxx is safer than other NSAIDs in patients taking warfarin.

Omission of Important Risk Information

Your promotional audio conferences fail to present serious and significant risks associated with Vioxx therapy. For example, your promotional audio conferences fail to state that Vioxx is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. You also fail to present the gastrointestinal (GI) warning about the possibility of serious GI toxicity such as bleeding, ulceration, or perforation in patients taking Vioxx. Moreover, you fail to present Vioxx's precautions for use in patients who have liver and kidney disease, information about patient populations in which Vioxx's use is not recommended, such as women in late pregnancy, and information about Vioxx's most common adverse events.

Unsubstantiated Superiority Claims

You make several unsubstantiated superiority claims for Vioxx throughout your promotional audio conferences. For example, in your June 16, 2000, audio conference, you claim that, "The importance of [VIGOR and CLASS] is that the data is going to really help change I believe the package inserts for [Vioxx and Celebrex] down the road because it really shows once again that they are safer than non-steroidals." Your suggestion that COX-2 inhibitors, including Vioxx, have an overall safety profile that is superior to other NSAIDs is misleading because such an advantage has not been demonstrated. In fact, in the VIGOR study the incidence of serious adverse events was higher in the Vioxx treatment group than in the naproxen treatment group (9.3% and 7.8% for Vioxx and naproxen, respectively). The results of safety analyses that were pre-specified in the protocol for the VIGOR trial, such as CHF-related adverse events and discontinuations due to edema-related adverse events, hepatic-related adverse events, hypertension-related adverse events, and renal-related adverse events were all numerically higher (in some cases statistically significantly higher) in the Vioxx treatment group than in the naproxen treatment group. Furthermore, your claim that the VIGOR and CLASS trials "show once again that they are safer than non-steroidals" is also misleading because it implies that the results of the VIGOR trial (i.e., patients on Vioxx had a significantly lower cumulative incidence of PUBs than patients on naproxen) can be applied to the entire class of NSAIDs.

In your June 16, 2000, audio conference you state, "...if you look at the thromboembolic events it's very clear that these selective COX-2 inhibitors have the benefit of not having platelet aggregation and

bleeding time, and therefore, can be used safely in terms of post-op and with Coumadin." This claim suggests that Vioxx is safer, or has fewer side effects, than other NSAIDs used in the post-operative setting because COX-2 inhibitors do not affect platelet aggregation and bleeding time. Vioxx has not been studied, however, in head-to-head trials prospectively designed to assess its safety compared to other NSAIDS in the post-operative setting. Your superiority claim is therefore misleading.

Further examples of your unsubstantiated superiority claims include your claim that, "In terms of half life Vioxx has a half life of 17 hours and is truly a once a day drug, whereas Celebrex has a half life of 11 hours and is a BID (twice a day) drug," stated in your June 16, 2000, audio conference. This claim is misleading because it suggests that Celebrex must be dosed twice a day for all of its approved indications. In fact, Celebrex is approved for use either twice a day, or once a day, for the treatment of osteoarthritis. Therefore, your claim that Celebrex is a "BID drug" is misleading.

Promotion of Unapproved Uses

Your audio conferences are misleading because they promote Vioxx for unapproved uses. For example, in your June 21, 2000, conference, you claim that in the VIGOR study, "...the Vioxx 50 milligrams a day and the Naprosyn, a gram a day, were absolutely equally effective in terms of treating the patients with rheumatoid arthritis." Your claim is misleading because it suggests that Vioxx is effective for the treatment of rheumatoid arthritis when this has not been demonstrated. The VIGOR study was not designed to assess the efficacy of Vioxx for the treatment of rheumatoid arthritis. Your claim that Vioxx is "absolutely equally effective" to naproxen in treating patients with rheumatoid arthritis is also misleading because this has not been demonstrated by adequate and well-controlled clinical studies, and because the VIGOR study was not capable of assessing their comparative effectiveness.

Your promotional audio conferences are also misleading because they suggest that Vioxx is safe and effective for other unapproved uses such as the prevention of cancer and invasive cancer, and for the treatment of Alzheimer's disease and gout. Examples of claims that promote Vioxx for unapproved uses, include, but are not limited to, your claims in your June 16, 2000 audio conference that, "...COX-2 seems to be able to interfere with...programmed cell death. Therefore, you get this increased cell growth which allows polps to form, cancer and then invasive cancer. And by blocking COX-2 you can actually prevent the development of colon polyps, cancer and invasive cancer." Additional examples include your claims that "So we tried it [Vioxx] after Vioxx was released and really within one or two pills acute attacks of gout were being shut down," and "Specifically, if you looked at potential uses of these drugs, the most exciting right now I guess in two areas, one is Alzheimer's disease...."

Press Release

We have identified a Merck press release entitled, "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx," dated May 22, 2001, that is also false or misleading for similar reasons stated above. Additionally, your claim in the press release that Vioxx has a "favorable cardiovascular safety profile," is simply incomprehensible, given the rate of MI and serious cardiovascular events compared to naproxen. The implication that Vioxx's cardiovascular profile is superior to other NSAIDs is misleading; in fact, serious cardiovascular events were twice as frequent in the VIOXX treatment group (101 events, 2.5%) as in the naproxen treatment group (46 events, 1.1%) in the VIGOR study.

Oral Representations

Merck sales representatives have engaged in false or misleading promotional activities that also minimize the potentially serious MI result observed in the VIGOR trial. Specifically, Merck sales representatives made false or misleading statements to DDMAC reviewers at two different professional meetings. At your exhibit booth during the 119th Annual Meeting of the Maryland Pharmacists Association (MPhA), in Ocean City, Maryland, June 9 – June 12, 2001, your representative stated that the increased MI rate seen in patients on Vioxx in the VIGOR study is due to the fact that naproxen works just like aspirin (i.e., inhibits clotting and platelet aggregation). In addition, during the Annual Meeting of the American Society of Health-System Pharmacists (ASHP), in Los Angeles, California, June 3 – June 6, 2001, your representative stated that Vioxx had a greater MI rate in the VIGOR trial because naproxen is cardioprotective, having platelet effects similar to aspirin. These statements made by your sales representatives are misleading for the reasons stated above.

Conclusions and Requested Actions

The promotional activities and materials described above minimize the potentially serious cardiovascular findings that were observed in the VIGOR study, minimize the Vioxx / Coumadin drug interaction, omit crucial risk information associated with Vioxx therapy, contain unsubstantiated comparative claims, and promote unapproved uses. On December 16, 1999, we also objected to your dissemination of promotional materials for Vioxx that misrepresented Vioxx's safety profile, contained unsubstantiated comparative claims, and lacked fair balance.

Due to the seriousness of these violations, and the fact that your violative promotion of Vioxx has continued despite our prior written notification regarding similar violations, we request that you provide a detailed response to the issues raised in this Warning Letter on or before October 1, 2001. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing all violative promotional activities, and the dissemination of violative promotional materials for Vioxx.

2. Issuing a "Dear Healthcare provider" letter to correct false or misleading impressions and information. This proposed letter should be submitted to us for review prior to its release. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who were, or may have been exposed to the violative promotion.

3. A written statement of your intent to comply with "1" and "2" above.

Your written response should be received no later than October 1, 2001. If you have any questions or comments, please contact Lesley Frank, Ph.D., JD, by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

Raymond V. Gilmartin
Merak & Co., Inc.
NDA 21-042

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9456 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Vioxx, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

(See appended electronic signature page)

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications